

TREATMENT AND PREVENTION OF TUBERCULOSIS BY TUBERCULIN IMMUNIZATION.

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A specific treatment for any infection must have first, some theoretical foundation which shall be based upon at least a little experimental evidence, and secondly, its value must finally depend upon results obtained from the clinical standpoint. The production of artificial immunity to tuberculosis was considered practically impossible of accomplishment because there is scarcely any clinical evidence that one attack protects from another: Certainly, some immunity must, of course, occur, otherwise the spontaneous recoveries as is often the case would be impossible. For the past fifteen years tireless and painstaking experimental work has been carried on with a view to elucidate the possibility of producing an immunity in the lower animals. It seems that the strongest and most lasting immunity that has been attained thus far is by vaccination with attenuated living bacilli, although the germ-free products and killed bacteria also have some value as an immunizing agent.

In attempting to formulate a method of immunization in the tuberculous subject, the study of the mechanism of artificial immunization in animals is imperative. At this juncture it seems pertinent to discuss briefly the different species of the tubercle bacillus, before taking up the immunity question, Robert Koch, in his masterly monograph published in 1884, in which he gave a long list of cultures of the tubercle bacillus isolated from tuberculous tissues in fowls, cattle and man, was unable to detect any difference among them, declaring that in all the cultures, whether taken from miliary tubercles, lupus or perlsucht, the tubercle bacillus behaved exactly the same. Within the last decade our knowledge of the nature of the tubercle bacillus has been greatly enhanced, until at the

present time several distinct species are recognized. These are grouped according to their sources into human, bovine, avian and the tubercle bacillus of cold-blooded animals. This last group of bacilli is of comparatively small importance to the warm-blooded animals, since they are unable to grow at temperatures approaching blood heat, thereby precluding any possibility of infection. The avian tubercle bacillus departs quite considerably from either the bovine or human types of bacilli. This is shown by the lack of susceptibility to certain animals, for example, the guinea pig, which is otherwise so sensitive to the inoculation of the mammalian bacilli, shows a marked degree of refractoriness to the avian type. On the other hand, while birds react very slightly, often producing only localized lesions to inoculations of the tubercle bacillus of human origin. Cases have been reported in the literature where the avian bacillus was isolated from the human being, but such cases are excessively rare. Rabinowitsch calls attention to the occasional occurrence of the avian bacillus in cattle, swine, horses and monkeys, etc., but Simon Flexner is of the opinion that they constitute a small source of danger in the spread of tuberculosis among mammals. To Theobald Smith is due the honor of first calling attention to the distinction in type existing between certain bacilli of human and of bovine origin. Later, in 1901, Robt. Koch startled the scientific world with his announcement "that tuberculosis in cattle offers no source of danger to the human being." He still adheres to his original conception as evidenced by the fact that he reiterated in his Nobel prize address, delivered in 1906: "Human tuberculosis and tuberculosis in cattle are so distinct from each other

that the latter is not to be feared as transmissible to man." It has been proved beyond all peradventure of a doubt that such a statement is not correct, but it has accomplished more than anything else towards stimulating researches throughout the civilized world. Theobald Smith characterized the bovine tubercle bacillus as possessing a greater degree of pathogenic power for mammals than the human bacillus. It also differs from the latter by certain peculiarities of cultural and physiological properties, and that it was impossible to transmute one type into the other under artificial conditions of cultivation. Most authorities agree that transformations of avian, bovine and human bacilli into each other is questionable, even if one variety of bacilli was cultivated for a long period of time in the body of an alien species. Repeated experiments show that tuberculous materials and cultures of tubercle bacilli of human origin when injected into cattle failed to produce a marked or a general tuberculous infection, even when the material was inoculated directly into the circulation.

It is not within the scope of this paper to discuss fully the different types of tubercle bacilli and their pathogenicity. With this statement we may take up the subject of immunity.

The animals which have been of special use for tests of immunity are rabbits, cattle, goats and guinea pigs, the latter being so susceptible to the tubercle bacillus that it is well nigh impossible to produce a high grade of immunity in them. Koch made the first important contribution to the subject of immunity in tuberculosis by means of his tuberculin. During several years following many experimenters had varying degrees of success in the production of immunity in the small animals by the use of tuberculin and attenuated cultures of the tubercle bacillus. The most convincing evidence of the favorable results of experimental immunity in tuberculosis was made by Trudeau as early as 1892. He

treated tuberculous iritis in the rabbit's eye by subcutaneous injections of tuberculin, which resulted in a retrogression of the lesion and an apparent healing took place, which, however, ultimately relapsed somewhat, though very slowly. He further found that guinea pigs, rabbits, previously injected with dead tubercle bacilli, live, on an average, longer than the control animals when subsequently inoculated. Trudeau went a step further. He protected rabbits from virulent tubercle bacilli by twice injecting them with an attenuated culture of bird tubercle bacilli subcutaneously at intervals of twenty-one generations, then the subsequent infection of the virulent mammalian bacilli was made into the anterior chamber of the eye. Of the protected rabbits, not one developed a tuberculous lesion, while the controls showed, in the course of a few weeks, a general inflammation of the structures of the eye, the inoculation wound became cheesy, followed later by a more or less complete destruction of the eye ball. DeSchweinitz a few years later reported certain experiments which he had made on guinea pigs and cattle. The former were inoculated with cultures of human tubercle bacilli cultivated for twenty generations. Their virulence was of very low grade to these animals, for it served to protect them against the later inoculation with tuberculous material from a cow. Other pigs, unprotected, were inoculated with the same material, became tuberculous and died in about seven weeks. These and other experiments clearly establish the protective influence exerted by the inoculation of the living attenuated bacilli to more lasting and of greater potency than the immunity obtained by the bacterial products.

Trudeau claims he has never been able to thoroughly protect guinea pigs against a virulent tubercle bacillus, nor has he ever succeeded in curing experimental tuberculosis in them. Behring, as well as Koch, claims to have protected guinea pigs against virulent

infection, but the details of their *modus operandi* are exceedingly meager. The successful immunization or cure of guinea pigs with the living or dead bacilli or their specific products has possibly been accomplished in rare instances. It can be argued in favor of such experiments that a single demonstrated positive result is far better evidence than countless negative ones, when we consider for a moment that the guinea pig is the most susceptible of all animals, that spontaneous recovery in them is unknown.

Behring, in his Nobel prize address, in the year 1901, announced that it was possible and feasible to vaccinate cattle against tuberculosis. His first experiments were efforts to immunize them by means of tuberculin, and later by other toxins from the tubercle bacillus; dead bacilli and attenuated cultures of the tubercle bacillus were also employed. His present plan of immunization, which has become a standard one, for it is furnished commercially, is as follows: Young calves, preferably twelve weeks old, are inoculated intravenously with a standard human culture. Three months later an increased quantity of said culture is again injected. Cattle so treated may be regarded as highly immune, as shown by inoculating them with a virulent bovine culture of tubercle bacillus, with no permanent ill effects resulting. But if unprotected animals were inoculated with the same culture, a generalized tuberculosis developed, producing death in a few weeks. Behring speaks of his vaccinated animals as being "Jennerized," and believes that immunity lasts for life. Simon Flexner, in his admirable monograph on immunity in tuberculosis, which was read before the second annual meeting of the National Association for the Study and Prevention of Tuberculosis, calls attention to the fact that McFadyen is entitled to the credit of the discovery equally with Behring of the immunization of cattle from tuberculosis. Neufeld, a pupil of Koch, and Behring, in discussing the priority of this

important question, asserts that while working under Koch's direction he found, as early as 1900, that large animals, the donkey and cattle, for instance, could be protected against the inoculation of a culture of virulent tubercle bacilli, which was always fatal to control animals. So it seems that the priority of this important subject is an open one. As a matter of fact, the principle employed is not new in experimental medicine, for it was practiced long years ago by the immortal Pasteur in vaccination against fowl cholera, anthrax, etc. In 1902, Pearson and Gilliland were not only able to confirm the results of the preceding investigators, but were able to carry the principles of the method a step further by endeavoring to bring about an arrest of the disease in cattle already suffering from tuberculosis. Flexner, in discussing this subject, states that "while it is unlikely that such a therapeutic use of vaccination will ever be made in veterinary practice, the facts are of considerable interest, especially in view of the somewhat similar means employed to arrest tuberculosis in man." If all young healthy cattle were vaccinated before tuberculosis sets in, it would seem that this disease could be entirely eradicated. The gain would be almost incalculable to agriculture. Furthermore, it would enlarge the possibilities of producing immunity in the healthy human subject if it was thoroughly demonstrated in the lower animals over a long period of time that such a procedure was entirely harmless. It seems that the most satisfactory and solid immunity obtained in cattle is produced by a living culture of tubercle bacilli of human origin; this, when injected two or three times, according to Behring, renders the animal immune for life. This statement has not been proved, but it is certain that immunity has lasted at least two years against the inoculation of a virulent culture of bovine tubercle bacilli.

I have had little experience in this form of immunity, but have contented myself with the use of the dead tubercle bacilli, killed at

their minimum thermal death point. My results are all that could be desired. I and my assistants have had under experimentation for the last two years two herds of Jersey cattle, twenty in one herd and twenty-eight in the other. Every year, previous to the last two years, at least two or three animals would die from some form of tuberculosis. Before instituting any form of vaccine treatment, we used tuberculin on every animal as a diagnostic test, which resulted in a positive reaction in six, thus showing that six cows had some form of tuberculosis out of the forty-eight, three tuberculous cows coming from each herd. The vaccine used was a virulent culture of tubercle bacilli of bovine origin, heated for one hour at 60 degrees C. The healthy animals were injected with five milligrams of the vaccine subcutaneously as an initial dose, followed one month later by ten milligrams, and three months later by twenty milligrams; the last dose was one hundred milligrams, which was given six months from the first injection. Two years have elapsed without a death from tuberculosis, except three, which belonged to the original six previously diagnosed as tuberculous by the tuberculin test. The three animals that were in the last stages were isolated while the remaining three, not far advanced, were allowed to run with the herd. Two of these have practically been cured (so far as we can determine as to symptoms, temperature, etc.) by the bovine vaccine. In treating the tuberculous cows, the method of Trudeau in treating tuberculous human beings was in a measure adhered to. We began with small doses and ran up to very high ones, injecting every week. Our initial dose was 1-100 of a milligram with double the dose at the next inoculation, and so on after the method of Trudeau. Of the six tuberculous cows, in which the above treatment was taken up by us, just two years ago, three have died, one will possibly succumb to the infection in the course of a month or so, while two are apparently well. We be-

lieve that the injection greatly prolonged life in at least three cows, while the two apparent recoveries were cases of a mild type; still we believe that the treatment aided very materially in their recovery.

All of the foregoing experiments by the different investigators unquestionably establish for tuberculosis the principle of artificial immunization, an achievement hitherto considered as impossible. Although this immunity in very susceptible animals may not be as frank and lasting as we would like, still experiments have proven that it undoubtedly prolongs life when a lethal dose of virulent bacilli be administered to the vaccinated animal as compared with a similar dose given to the unprotected one. Again, it has been shown in the larger animals suffering from localized tuberculosis that by a systematic administration of a tubercle vaccine that there is a retardation in the development of the disease, producing reparative changes in the lesions, and if in the earlier stages often a complete recovery results.

We may ask the pertinent question, why should we not expect just as good if not better results in man than has been accomplished in the lower animals? We know that the human being is not as susceptible to this disease as most of the animals experimented on, because the normal resisting power of the body overcomes the invading organisms, and that spontaneous recoveries in man are exceedingly common. These facts offer us some hope in the future. Already Trudeau has given us some very encouraging figures, showing the comparison of the post-discharge mortality between patients treated and those that were untreated with tuberculin at the Saranac Lake Sanatorium. He says that eighteen per cent more of treated incipient cases are living than of the untreated, while twenty-five per cent. more of advanced cases who received tuberculin are living than of those who did not submit themselves to the inoculation of this agent. It would be en-

tirely feasible to administer a series of inoculations of the vaccine to certain individuals who have a tendency to consumption, even though they had not the disease at the present time. Given a child that is listless, with a pallid skin and flabby flesh, a tendency to inflammations of mucous membranes, in other words a vitiated state of the tissues, a tendency to tuberculosis. In such an individual the tuberculin treatment is imperatively indicated.

The Tuberculins:—The term tuberculin is a broad one, which includes quite a number of different preparations. The first used was Koch's original tuberculin "T. O.," called also "old" tuberculin, to distinguish it from his more recent product, "new" tuberculin.

The "old" tuberculin is the concentrated germ-free culture medium (glycerin bouillon), in which the tubercle bacilli were allowed to grow for several weeks.

The Tuberculin (Dénys) Bouillon Filtrate "B. F." is a product rather similar to the "T. O.," but differs from it in that no heat is used in its preparation and that the bacilli are grown in bouillon.

The Tuberculin "R.," "T. R." or "Tuberculin Residue" is prepared by growing a virulent culture of tubercle bacilli. They are dried in the dark in vacuo and then pulverized. The powder thus obtained is suspended in distilled water and centrifugated at very high speed for about thirty minutes. The water is then drawn off and discarded and the bacterial residue is again dried in vacuo as above and treated in the same manner. This is done several times. It is supplied in liquid form, containing two milligrams of the powder to the c. c. of twenty per cent. glycerin solution.

Bacillen Emulsion "B. E." This is Koeh's latest product, which he has suggested for active immunization. It consists of an emulsion of the ground-up tubercle bacilli in equal parts of glycerin and normal saline solution. There are many other preparations used, viz: the Antiphisn (Klebs), Hunter's modification

of Old Tuberculin, the watery extract of tubercle bacilli (Von Ruck), the "P. T. O." (Spengler) and many others. The action of all these various tuberculins, according to Pottenger, is similar in part, yet different. Some are much safer to use than others and seem to produce better results than others. His experience with the "P. T. O." (Spengler) is very encouraging. This product is made from bovine bacilli. Pottenger claims that "P. T. O." will immunize against the human toxin much more strongly than the human will against the bovine toxin. He further states that its use will raise the agglutinating power of the blood to a much higher degree than the human tuberculins, and that this power of agglutination will last longer. Taking all the tuberculins into consideration it would seem, theoretically, that the Bacillen Emulsion would offer the most suitable agent to use in order to produce the most marked grade of immunity to the various activities of the tubercle bacillus. It contains not only the body substance of the bacteria but the toxins of the tuberculin as well. The old tuberculin produces antitoxic immunity, while the "B. E." produces bactericidal and antitoxic immunity. Professor Theobald Smith, as a result of his recent studies on animals, suggests virulent uncrushed tubercle bacilli, killed at sixty degrees C., as the best vaccine to be tried in attempts at immunizing human beings. Personally, I have used only the "Bacillen Emulsion" for therapeutic administration, and the old tuberculin, as well as the "B. F.," for diagnostic purposes. My results have been so gratifying that I have no reason for changing to other preparations. I have observed that after a change from one make of the "Bacillen Emulsion" to another (especially in some patients, where they seem not to be doing well) one will be surprised sometimes to find them again on the road to health after the measures previously applied seemed to have reached the limit of their efficacy.

The method employed in the administration of the "Bacillen Emulsion" is according to Trudeau's plan. It is not possible to give in detail the plan for the lack of space, but suffice it to state that he begins with extremely small doses, 1-10,000 of a milligram, and gradually increases, so gradually and at such intervals as to carry the patient to full doses with as little disturbance as possible. By such a method individuals can take ten thousand times stronger than the original dose without any effect. Injections are given about twice a week, of course depending upon the symptoms of the patient, for herein lies the secret of success in the treatment. This plan may be called the practical or clinical method in contradistinction to the scientific or laboratory method, as advocated by Wright and his followers. Wright's method of immunization is based essentially on the determination of the index. In a previous communication about a year and a half ago I advocated the administration of tuberculin governed by the opsonic index; certainly such a method is a brilliant contribution to our knowledge of the mechanism of artificial immunization, but it takes much time and work, necessary in determining the index, which makes it impractical of application in the treatment of tuberculosis by such a method. I find myself slowly drifting to the clinical symptomatology, not only by reason of its practicability of administration, but also by the just as good results that are being obtained by this method of administration as compared with that of Wright.

In conclusion I may state:

(1) Experiments on animals demonstrate the possibility of creating immunity to tuberculosis by the use of the tuberculin:

(2) I am of the opinion that the time is not far distant when individuals showing a tuberculous tendency will submit themselves to the repeated injections of some form of tuberculin, as a means of prophylaxis against this disease.

(3) The clinical method in the administration of tuberculin is far preferable to the one advocated by Wright in which the estimation of the opsonic index is essential.

(4) Tuberculin therapy is proving an essential aid in the treatment of tuberculosis, especially as an adjuvant to the hygienic-dietic open air treatment.

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